

# TREATMENT OF GONORRHOEA WITH TERRAMYCIN\*

## A COMPARISON WITH PENICILLIN

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Terramycin has been used orally for the treatment of gonorrhoea by a number of workers, including Caldwell and others (1950), Robinson (1950, 1952), Sayer and others (1951), and Schoch and Alexander (1950). In general, the results obtained by single doses of 0.5–1.0 g. have not been entirely satisfactory. Putkonen (1951), for example, cured only 45 out of 55 patients with 1.0 g., and the administration of two doses of 0.5–1.0 g. each at an interval of 6 hours has been reported to give better results. Thus Wright and others (1951) had 88.7 per cent. of 120 patients cured by two doses of 0.5 g., and Hendricks and others (1950) claimed that all of a group of fifteen were cured by two doses of 1.0 g. A comparison of terramycin and aureomycin, in doses of 1.0–2.0 g., was attempted by Beinfeld and others (1951). Of 130 patients treated with terramycin, 106 were followed-up and there were five relapses. Of 130 others treated with aureomycin, 107 were followed-up and there were four relapses.

### Present Investigations

The trials with terramycin reported here have been in progress since November, 1950. Several schedules involving a total dose of 2.0 g. given orally have been tried :

- (1) 1 g. given at once, followed by a further dose of 1 g. after 6 hrs (Willcox, 1951).
- (2) One capsule (250 mg.) given four times a day for 2 days (Willcox, 1952).
- (3) Two capsules (500 mg.) given four times a day for one day (Willcox, 1953a).
- (4) 1 g. given at once, followed by one capsule (250 mg.) four times a day for one day (Willcox, 1953b).
- (5) A single oral dose of 2 g. (Willcox, 1953c).

The numbers previously reported have been added to and a total of 202 cases is now presented.

The results of treatment are compared with those in 223 cases of gonorrhoea treated during the same period with single injections of 150,000 units procaine penicillin. Basic details of the two groups are given in Table I.

TABLE I  
BASIC DETAILS OF PATIENTS IN TWO TREATMENT GROUPS

| Therapy                                       |                         | Terramycin<br>(202 cases)     | Penicillin<br>(223 cases) |     |
|---|-------------------------|-------------------------------|---------------------------|-----|
| Sex   | Male                    | 192                           | 223                       |     |
|   | Female                  | 10                            | —                         |     |
| Race  | White                   | 179                           | 204                       |     |
|   | Negro                   | 23                            | 19                        |     |
| Marital Status                                | Married                 | 63                            | 63                        |     |
|   | Single                  | 139                           | 160                       |     |
| Average Age (yrs)                             |                         | 30.1                          | 28.7                      |     |
| Previous<br>History of<br>Venereal<br>Disease | None                    | 91                            | 104                       |     |
|   | Gonorrhoea              | 135                           | 214                       |     |
|   | Non-specific urethritis | 19                            | 21                        |     |
|   | Syphilis                | 20                            | 11                        |     |
|   | Other sores             | 1                             | 5                         |     |
| Serum Tests                                   | Syphilis                | WR negative, Kahn<br>negative | 191                       | 220 |
|   |                         | WR negative, Kahn<br>positive | 8                         | 1   |
|   |                         | WR positive, Kahn<br>positive | 3                         |     |
|   |                         |                               |                           |     |
|   | Gonorrhoea              | GCFT negative                 | 147                       | 81  |
|   |                         | GCFT doubtful                 | 4                         | 1   |
|   |                         | GCFT positive                 | 12                        | 5   |
|   |                         | GCFT not done                 | 39                        | 136 |
|   |                         |                               |                           |     |

### Results

During the sulphonamide era an observation period of 3 months after the treatment of gonorrhoea was considered amply sufficient, and any later extension of this time was concerned solely with the exclusion of developing syphilis. For this reason, in the analysis of the results, it is considered proper to define any gonococcus-positive 'failure' noted after 3 months as a re-infection. No other attempt being made to differentiate relapse from re-infection,

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the outcome of the two treatments is shown in Table II.

TABLE II  
RESULTS OF TREATMENT WITHOUT REGARD TO  
RE-INFECTION

| Therapy    | Cases Treated | Cases Followed | 'Failures' within 3 Months | Per cent. failures in those Followed |
|------------|---------------|----------------|----------------------------|--------------------------------------|
| Terramycin | 202           | 170            | 22                         | 12.9                                 |
| Penicillin | 223           | 200            | 38                         | 19.0                                 |

In fact, however, nearly all of the failures noted after one month were believed to be re-infections on the criterion of admitted new intercourse with a person who, on being secured for examination, was found to be suffering from gonorrhoea. In Table III, in which by cumulating the failure rate some allowance is made for the differences in follow-up, the suspected relapses have been differentiated from the re-infections.

Thus, although the ultimate results of treatment with terramycin are apparently as good as those of penicillin in the dosage given, there were more failures with terramycin in the days immediately following treatment than with penicillin. It is

likely, therefore, that most of the 'relapses' with penicillin after 28 days were also re-infections. As it stands the results of treatment at one month were in favour of penicillin, and at 3 months in favour of terramycin.

A comparison of the terramycin schedules is shown in Table IV.

Schedule IV (1 g. followed by one capsule (250 mg.) four times a day for one day) proved to be the best of those tested, while Schedules I and V were the least successful.

### Non-Specific Urethritis

Of particular interest is the comparison of the incidence of non-specific infections (Table V, opposite). Penicillin, unlike terramycin (Willcox and Findlay, 1952), is not usually effective in the treatment of non-specific urethritis. Thus, if non-specific urethritis has an infective aetiology, one might expect that it would be aborted during the terramycin treatment of gonorrhoea.

It is possible that some of the re-treatments for non-specific urethritis made during the first week

TABLE III  
CUMULATIVE FAILURE RATE, EXCLUDING OBVIOUS RE-INFECTIONS

| Therapy    | Length of Follow-up | Number Followed | Re-infections | Relapses | Cumulative Percentage Relapses |
|------------|---------------------|-----------------|---------------|----------|--------------------------------|
| Terramycin | 0 .. .. .           | 202             | —             | —        | —                              |
|            | 1-7 days .. .. .    | 170             | 1             | 11       | 6.5                            |
|            | 8-14 days .. .. .   | 131             | 1             | 3        | 8.8                            |
|            | 15-21 days .. .. .  | 114             | —             | 1        | 9.7                            |
|            | 22-28 days .. .. .  | 100             | 1             | 1        | 10.7                           |
|            | 1-2 mths .. .. .    | 90              | 1             | —        | 10.7                           |
|            | 2-3 mths .. .. .    | 58              | 2             | —        | 10.7                           |
|            | Over 3 mths .. .. . | 31              | 1             | —        | —                              |
|            | Total .. .. .       |                 | 7             | 16       | At 22-28 days 10.7             |
| Penicillin | 0 .. .. .           | 223             | —             | —        | —                              |
|            | 1-7 days .. .. .    | 200             | —             | 1        | 0.5                            |
|            | 8-14 days .. .. .   | 152             | 1             | 6        | 4.4                            |
|            | 15-21 days .. .. .  | 128             | 3             | 2        | 6.0                            |
|            | 22-28 days .. .. .  | 118             | 5             | 2        | 7.7                            |
|            | 1-2 mths .. .. .    | 100             | 4             | 5        | 12.7                           |
|            | 2-3 mths .. .. .    | 68              | 7             | 2        | 15.6                           |
|            | Over 3 mths .. .. . | 48              | 22            | —        | —                              |
|            | Total .. .. .       |                 | 42            | 18       | At 22-28 days 7.7              |

TABLE IV  
COMPARISON OF TERRAMYCIN SCHEDULES

| Dosage Schedule  | Cases Treated | Cases Followed | Total 'Failures' within 3 months | Relapses | Re-infections | Percentage Relapsing of Cases Followed |
|--|---------------|----------------|----------------------------------|----------|---------------|--|
| I. Two doses of 1 g. at interval of 6 hrs .. .. .        | 30            | 26             | 5                                | 4        | 1             | 15.4                                   |
| II. 250 mg. 4 times daily for 2 days .. .. .             | 44            | 38             | 7                                | 3        | 4             | 7.9                                    |
| III. 500 mg. 4 times in one day .. .. .                  | 46            | 40             | 4                                | 3        | 1             | 7.5                                    |
| IV. 1 g. at once plus 250 mg. 4 times in one day .. .. . | 45            | 37             | 1                                | 1        | —             | 2.7                                    |
| V. Single dose of 2 g. .. .. .                           | 37            | 29             | 5                                | 5        | —             | 17.2                                   |
| Totals .. .. .   | 202           | 170            | 22                               | 16       | 6             | 9.4                                    |

TABLE V  
INCIDENCE OF SUBSEQUENT NON-SPECIFIC URETHRITIS

| Therapy    | Follow-up     | Cases Followed | Non-Specific Recurrences | Cumulative NSU Rate per cent.                |
|------------|---------------|----------------|--------------------------|--|
| Terramycin | 0 ..          | 202            | —                        | —  |
|            | 1-7 days ..   | 170            | 1                        | 0.6  |
|            | 8-14 days ..  | 131            | 3                        | 2.9  |
|            | 15-21 days .. | 114            | 3                        | 5.5  |
|            | 22-28 days .. | 100            | 3                        | 8.5  |
|            | 1-2 mths      | 90             | 4                        | 12.9   |
|            | 2-3 mths      | 58             | 1                        | 14.6   |
|            | over 3 mths   | 31             | 4                        | Cumulative rate at 2-3 months 14.6 per cent. |
| Penicillin | 0 ..          | 223            | —                        | —  |
|            | 1-7 days ..   | 200            | 11                       | 5.5  |
|            | 8-14 days ..  | 152            | 6                        | 9.4  |
|            | 15-21 days .. | 128            | 2                        | 11.0   |
|            | 22-28 days .. | 118            | 4                        | 14.4   |
|            | 1-2 mths      | 100            | 3                        | 17.4   |
|            | 2-3 mths      | 68             | 3                        | 21.8   |
|            | over 3 mths   | 48             | 6                        | Cumulative rate at 2-3 months 21.8 per cent. |

after the treatment of the gonorrhoea were not strictly necessary and were undertaken merely for a residual urethritis which would have disappeared spontaneously without further treatment. *If these are excluded the non-specific urethritis rate for the terramycin-treated group (14 per cent.) is comparable with the 16.3 per cent. for the penicillin-treated group, and there is no significant difference.*

Of the nineteen cases of non-specific infections noted in the terramycin-treated series, sixteen had uncomplicated urethritis, two had persistent pus in the prostatic smears, and in one the urethritis was complicated by Reiter's syndrome (at 26 days). Of the 35 cases in the penicillin-treated series, 31 had uncomplicated urethritis, one was complicated by cystitis, one by Reiter's syndrome (at 10 days), and in two cases there was persistent pus in the prostatic smear. Thus neither penicillin nor terramycin prevented the development of Reiter's syndrome.

The incidence of non-specific urethritis following the different terramycin schedules is shown in Table VI. Cases occurring more than three months after the treatment of gonorrhoea have been excluded.

The urethritis rate was thus very similar with all schedules except Schedule V, which apparently gave better results. As the highest, if transient, serum levels of terramycin would have been obtained on this schedule, it is considered that it will be worth while to investigate another series employing a higher dosage of terramycin.

### Summary and Conclusions

(1) 202 patients with acute gonorrhoea were treated with one of five dosage schedules of oral terramycin (total dosage 2 g.). The results were compared with those in 223 patients treated with a single intramuscular injection of 150,000 units of procaine penicillin.

(2) The results of the two methods were comparable, whether suspected re-infections were included as "failures" or not.

(3) The most successful terramycin schedule was that consisting of 1 g. given immediately and followed by 250 mg. four times in one day. There was only one gonococcus-positive failure in 37 cases followed out of 45 patients treated.

(4) The incidence of subsequent non-specific urethritis was also compared. No significant difference was noted between the terramycin-treated and the penicillin-treated groups. Terramycin, in the dosage given, was no more successful than penicillin in preventing non-specific urethritis or Reiter's syndrome.

(5) The terramycin schedule which was followed by the least non-specific urethritis was that consisting of 2 g. in a single oral dose (only one case in 29 followed out of 37 treated). As this schedule was likely to have produced the highest, if transient, terramycin serum levels, it is considered that it will be worth while to continue this part of the investigation employing a higher dosage.

The terramycin used in this study was kindly provided by Charles Pfizer and Co. Inc., Brooklyn, New York. Much of this material was studied during the author's term of office as Insole Research Scholar of the British Medical Association.

TABLE VI  
NON-SPECIFIC URETHRITIS RELATED TO TERRAMYCIN SCHEDULES

| Dosage Schedule   | Cases Treated | Cases Followed | NSU before 3 months | Percentage of Cases Followed |
|---|---------------|----------------|---------------------|------------------------------|
| I. 2 doses of 1 g. at interval of 6 hrs .. ..           | 30            | 26             | 2                   | 7.7                          |
| II. 250 mg. four times daily for 2 days .. ..           | 44            | 38             | 4                   | 10.5                         |
| III. 500 mg. four times in one day .. ..                | 46            | 40             | 4                   | 10.0                         |
| IV. 1 g. immediately plus 250 mg. four times in one day | 45            | 37             | 4                   | 10.8                         |
| V. Single dose of 2 g. .. ..                            | 37            | 29             | 1                   | 3.5                          |
| Totals .. ..  | 202           | 170            | 15                  | 9.4                          |

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